Update in
Anaesthesia

Perioperative management of patients on warfarin and the new oral anticoagulants

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Summary
Correct management of a patient's anticoagulation during the perioperative period is of great importance.

Surgery causes hypercoagulability and most patients are at increased risk of venous thromboembolism.

Interruption of anticoagulation increases this risk further and must be balanced against the risk of surgical bleeding.

INTRODUCTION

Among patients over 80 years, 23% of those who suffer a stroke have atrial fibrillation, and so the number of patients on anticoagulation therapy is growing. Around one in six of these anticoagulated patients will require interruption of therapy for a surgical procedure each year.[1]

Perioperative management of anticoagulant therapy is constantly evolving, with the primary aim being a balance between reducing the risk of systemic arterial and venous embolism and reducing perioperative bleeding risk. The traditional strategy to 'bridge' interrupted warfarin therapy for atrial fibrillation with the administration of low-molecular-weight heparin is under review, following the results of large and influential studies such as the BRIDGE trial.[1] The use of novel oral anticoagulants (NOACs) is also increasing and so it is crucial to understand both the pharmacokinetics of these drugs and their use in the perioperative period. This article aims to give a concise update of perioperative anticoagulation and to guide readers on the perioperative management of patients on NOACs.

INDICATIONS FOR ANTICOAGULATION

Oral anticoagulation is indicated in the following conditions.

Warfarin[2]

- Prophylaxis of systemic embolism in patients with rheumatic heart disease and atrial fibrillation.
- Prophylaxis of systemic embolism after insertion of prosthetic heart valves.
- Prophylaxis and treatment of venous thrombosis and pulmonary embolism.
- Transient cerebral ischaemic attacks.

NOACs[3–6]

- Prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement (edoxaban not yet licensed for this indication).
- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation.
- Treatment of deep vein thrombosis and pulmonary embolism, and prevention of recurrent deep vein thrombosis and pulmonary embolism in adults.
- Rivaroxaban also licensed in acute coronary syndrome for prevention of artherothrombotic events in combination with aspirin and clopidogrel or ticlopidine.

CLINICAL RISK PREDICTION[7]

The clinical prediction tool we have used for assessing stroke risk factors in a patient with non-rheumatic atrial fibrillation during the perioperative period is $CHADS_2$. Each score (0, 1, 2) represents a risk contributing to the likelihood of an embolic event as outlined in Table 1.

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Table 1. *$CHADS_2$ tool*

Risk factor	Score
Congestive heart failure or left ventricular dysfunction	1
Hypertension blood pressure consist of above 140/90 mmHg or treated hypertension on medication	1
Age greater than 75 years	1
Diabetes mellitus	1
Stroke or transient ischaemic attack or thromboembolism	2

The initiation of anticoagulation is recommended in patients with a $CHADS_2$ score of 2 or more.

THE CLOTTING CASCADE

The classical view of the clotting cascade (Figure 1) with intrinsic and extrinsic pathways has been useful for interpreting *in vitro* tests of coagulation but is felt to be outdated and potentially inaccurate. It is now thought that generation or exposure of tissue factors at the wound surface along with interaction with factor 7 is the main event that initiates clotting and that the cascade is much more of a dynamic and interwoven process.

WARFARIN

Warfarin is the most widely prescribed anticoagulant in the UK, and was first available in the 1950s.[9] It is a vitamin K antagonist and inhibits the reduction of vitamin K to its active form, hydroquinone.

Clinical coagulation tests commonly used for warfarin

- **Prothrombin time (PT)** is the time taken (in seconds) for blood to clot in the presence of tissue factor. It assesses the extrinsic and common pathway of the clotting cascade and can vary depending on the situation and laboratory equipment used.
- **The international normalised ratio (INR)** was developed to eliminate the variation caused by different laboratories by comparing a PT against an internationally recognised standard PT control sample and expressing the result as a dimensionless ratio. Thus, an INR would be the same on a given sample regardless of the laboratory or equipment used.[8]

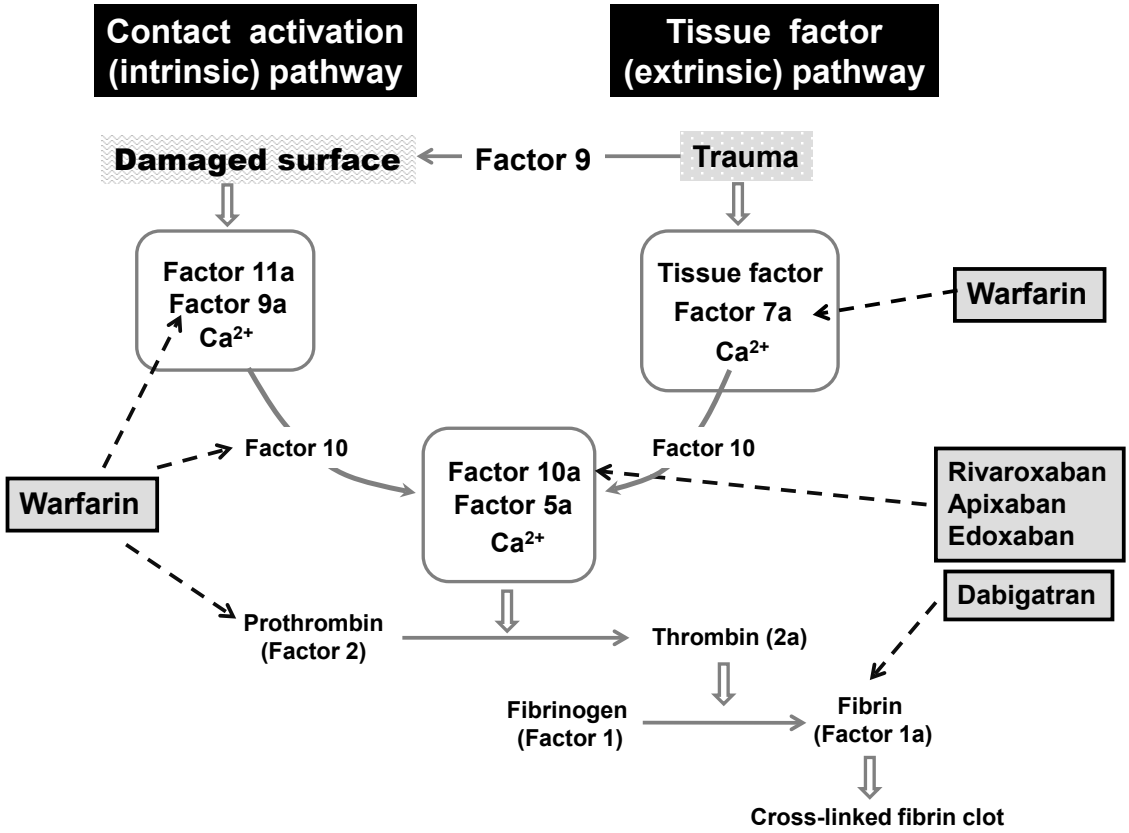

Figure 1. *A highly simplified view of the traditional clotting cascade. The sites of action of warfarin and the novel anticoagulants are shown. This format does conform with the information that laboratory coagulation tests provide; however, in the last 15 years, a cell-based model of coagulation that better explains coagulation function and pathology that is seen in clinical practice has been proposed. Further details of this theory are available in the following paper: Hoffman M and Monroe DM. A cell-based model of hemostasis. Thrombosis and Haemostasis 2001;* ***85****: 958–65*

Hydroquinone binds competitively to active clotting factors 2, 7, 9 and 10 and anticoagulant proteins C and S, decreasing their activities. Its effect can be measured using the prothrombin time or INR.[9]

Pharmacokinetics

Warfarin is almost completely absorbed from the gut with peak blood concentration reached within 4 hours. Peak time of action is 48–72 hours, and anticoagulation effect generally occurs within 24 hours. However, peak effect may be delayed 72–96 hours.[2]

Side-effects

The most common side-effect of warfarin is adverse bleeding. By inhibiting protein C, warfarin can cause a paradoxical activation of coagulation, leading to thrombosis and, rarely, erythematous swollen skin patches, leading to ecchymosis, infarction and skin necrosis. It is also contraindicated in the first and third trimesters of pregnancy as it crosses the placenta and is teratogenic.[2]

Drug interactions

Warfarin interacts with multiple other drugs, particularly those that inhibit or induce cytochrome P450 (CYP450), as well as with cranberry juice. Inducers of cytochrome P450 will generally decrease the INR and inhibitors will increase it (Table 2).

Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, potentiates the effect of warfarin through displacement of warfarin from its binding site on albumin and also through inhibition of platelet function.

Therapeutic use

For effective prevention of stroke, in patients in atrial fibrillation the time spent in the therapeutic INR range (TTR) should be monitored over a period of months. Ideally TTR should be greater than 65%. If the TTR is less than 65%, patient factors contributing to poor anticoagulation control should be addressed. Examples of such factors are:

- cognitive dysfunction
- adherence to prescribed therapy
- illness
- interacting drug therapy and
- lifestyle factors such as diet and alcohol consumption.

If no reversible factors can be identified and the TTR cannot be improved, an alternative method of stroke risk prevention should be employed.

Table 2. *Common inhibitors and inducers of cytochrome P450*

Inhibitors	Inducers
Sodium valproate	Carbamazepine
Isoniazid	Rifampicin
Cimetidine	Alcohol
Ketoconazole	Phenytoin
Fluconazole	Griseofulvin
Alcohol	Phenobarbital
Chloramphenicol	Sulphonylureas
Erythromycin	
Sulphonamides	
Ciprofloxacin	
Omeprazole	
Metronidazole	

WARFARIN BRIDGING THERAPY

Most hospitals have policies to guide bridging therapy with warfarin. The surgeon who books the patient for surgery should assess the need to interrupt anticoagulant therapy based on the bleeding risk posed by surgery; skin biopsies, minor dental extraction, cataract surgery and some cardiac procedures are associated with a low risk of bleeding whilst on therapeutic warfarin. Major procedures such as abdominal hysterectomy, endoscopic resection of prostate, lumbar discectomy, thyroidectomy, total joint replacement, lung operations, colonic resection, and radical neck dissection are high-risk operations for bleeding. Typically, warfarin is stopped 4–5 days prior to surgery. The type of bridging therapy offered is based on the patient's thrombotic risk in the absence of therapeutic warfarin (see Table 3).

The BRIDGE trial[1]

In June 2015, the results of this randomised, double-blinded, placebo-controlled trial were published. The aim of the study was to determine if avoiding bridging in patients with atrial fibrillation undergoing elective procedures decreased the risk of perioperative bleeding and/or increased the risk of arterial thromboembolism. The trial included 1884 patients with atrial fibrillation (valvular and non-valvular) with at least one risk factor for stroke (hypertension, age > 75 years, congestive cardiac failure, diabetes, previous ischaemic stroke/transient ischaemic attack).

The results showed that, at 37 days postoperatively, there was no increase in thromboembolic complications but that there was a significant decrease in the amount of perioperative bleeding in patients who did not receive bridging therapy. The incidence of arterial thromboembolism was 0.4% in the no-bridging group and 0.3% in the bridging group, a difference that was not statistically significant different ($P = 0.01$ for non-inferiority, $P = 0.73$ for superiority). Among patients who experienced arterial thromboembolism, 70% had undergone a minor procedure, the median time to event was 19 days and the average $CHADS_2$ score was 2.4.

Major bleeding occurred in 1.3% of patients in the no-bridging group and in 3.2% in the bridging group.

There was no significant difference between the groups with regard to myocardial infarction, venous thromboembolism or death. The mechanisms of perioperative arterial thromboembolism may be closely related to factors such as the type of procedure and to intraoperative alterations in blood pressure. The premise that warfarin interruption leads to rebound hypercoagulability and that the milieu of the procedure confers a prothrombotic state, which in turn leads to arterial thromboembolism, is not supported by the results of this trial.

Limitations of the BRIDGE trial

A few groups were under-represented in the study sample, for example patients with $CHADS_2$ scores of 5–6 and patients undergoing carotid endarterectomy, major cancer surgery, cardiac surgery and neurosurgery, and patients with mechanical heart valves.

Current guidance following the BRIDGE trial

For warfarinised patients with atrial fibrillation, no bridging is required. Bridging should be considered only if the $CHADS_2$ score is greater than 4 or there is history of a CVE (including TIA) within the preceding 3 months.[10,11]

Table 3 takes into account recent updates in evidence.

PERIOPERATIVE MANAGEMENT OF THE NOACS[12]

The European Society of Cardiology (ESC)[13] recently recommended that surgical procedures be classified in three categories:

- interventions not requiring discontinuation of anticoagulation (dental, ophthalmology procedures);
- intervention with low bleeding risk (prostate or bladder biopsy, angiography, pacemaker insertion);
- high bleeding risk procedures (spinal, epidural anaesthesia, lumbar puncture, cardiothoracic surgery, abdominal surgery, major orthopaedic surgery, liver biopsy, transurethral resection of the prostate and kidney biopsy).

The ESC guidelines advise the NOACs be stopped 24 hours before a low bleeding risk procedure, and between 48 and 96 hours before a procedure with a high bleeding risk.

DABIGATRAN

Dabigatran has predictable pharmacokinetics and can usually be stopped close to the time of surgery. Bridging is not currently recommended. Check renal function preoperatively and use results to plan the timing of the last dose presurgery (see Table 5).

Postoperatively, if adequate haemostasis is achieved, dabigatran can be restarted at the preoperative dose when haemostasis achieved. Alternatively, depending on the risk of a venous thrombotic event (VTE), prophylactic low-molecular-weight heparin (LMWH) can be given 6–8 hours after surgery.

RIVAROXABAN, APIXABAN AND EDOXABAN

Rivaroxaban, apixaban and edoxaban also have predictable pharmacokinetics and can be stopped close to the time of surgery; consequently, patients receiving these medications do not require bridging. The advice is to stop these agents 48 hours before surgery. Rivaroxaban/apixaban/edoxaban can be restarted at the same dose the patient was receiving preoperatively as soon as adequate haemostasis is achieved. The factor Xa inhibitor betrixaban is currently in phase III trials, but it is thought to have similar pharmacokinetics to other factor Xa inhibitors. Owing to lack of information we cannot safely give recommendations on stopping this anticoagulant.

REGIONAL ANAESTHESIA AND ANTICOAGULATION

Regional anaesthesia is an invaluable option for many procedures, either in place of or combined with general anaesthesia. Serious complications in patients with normal coagulation are very rare. For example, in the third UK national audit project, the incidence of vertebral canal haematoma after neuraxial blockade was 0.85 per 100 000 cases.[14] The extent to which the risk of haemorrhagic complications is increased in patients with abnormalities of anticoagulation is unquantifiable, but is likely to be small.[15] Table 6 shows the latest recommendations for performing regional anaesthesia in patients on medications that render their coagulation abnormal.

In the UK, the Association of Anaesthetists of Great Britain and Ireland (AAGBI) recognises a spectrum of increased risk with different regional techniques. Risk relates to complications such as bleeding, haematomas and compression of other structures leading to potential airway compromise or tissue ischaemia. Epidurals and spinals are thought to be associated with the highest risk of complications, with the risk decreasing as the blocks become more peripheral.

ASSESSMENT OF COAGULATION WITH NOACS

Conventional tests of coagulation

The NOACs are an appealing alternative to warfarin as they do not need to be monitored and they have been shown to be as efficacious as, or indeed superior to, warfarin in preventing stroke or systemic embolisation. However, clinicians remain wary of these agents because of the lack of options for reversal of their anticoagulant effects in situations where this is imperative – such as emergency surgery and/or haemorrhage.[16]

The activated partial thromboplastin time (aPTT) is a measure of the activity of the intrinsic pathway of the coagulation cascade.

Table 3. *Assessment of thrombotic risk and need for bridging therapy*[11,12]

Low risk of thrombosis	
Bileaflet AVR without AF, hypertension, stroke/TIA, diabetes, CCF, or age >75	No bridging
	Check that INR on day of surgery is < 1.5
Single VTE > 1 year ago	Postoperative VTE assessment for prophylaxis
Atrial fibrillation with CHADS2 score of 1–4	Restart warfarin post operation if haemostasis adequate
Moderate risk of thrombosis	
VTE > 3 months ago but < 1 year	Bridge only if thrombotic risk > bleeding risk
Recurrent VTE	If required, stop warfarin 4–5 days prior to surgery
Active cancer (treatment < 6 months or palliative)	Start prophylactic LMWH once daily 2 days after stopping warfarin
	Give last dose of LMWH 24 h pre-operatively
	Post operation: check adequate haemostasis
	Restart LMWH 6–8 hours post-operatively (may be delayed in high-risk bleeding)
	Continue bridging therapy until INR therapeutic
Bileaflet AVR with AF, hypertension, stroke/TIA, diabetes, CCF or age >75	Stop warfarin 4–5 days prior to surgery
	Start therapeutic LMWH once daily 2 days after stopping warfarin
	Give last dose 24 hours preoperatively
	Post operation: check adequate haemostasis. Give therapeutic LMWH 6–8 hours post-operatively (may be delayed in high-risk bleeding)
	Continue bridging therapy until INR in therapeutic range
High risk of thrombosis	
Mitral valve replacement	Stop warfarin 5 days prior to surgery
Older AVR (with tilting disc)	Start therapeutic LMWH once daily 2 days after stopping warfarin
Any mechanical valve with stroke/TIA <6 months	Give last dose 24 hours preoperatively
	Post operation: check adequate haemostasis. Give therapeutic LMWH 6–8 h post-operatively (may be delayed in high-risk bleeding)
	Continue bridging therapy until INR in therapeutic range
AF with stroke/TIA/mitral stenosis/arterial embolism < 3 months	Stop warfarin 5 days prior to surgery
	Start therapeutic daily LMWH 2 days after stopping warfarin
	Give last dose as a half-dose 24 hours preoperatively
	Post operation: check adequate haemostasis. Give therapeutic LMWH at 18.00 hours on first postoperative day
	Continue bridging therapy until INR in therapeutic range
Star–Edwards (ball and cage) AVR	Discuss with cardiology, as unfractionated heparin infusion may be required owing to high risk of thrombosis
VTE < 3 months	Defer surgery if possible. If not possible, consult with haematology as may require therapeutic dose LMWH or an inferior vena cava filter

AF, atrial fibrillation; AVR, aortic valve replacement; CCF, congestive cardiac failure; LMWH, low molecular weight heparin; TIA, transient ischaemic attack; VTE, venous thrombotic event.

Whilst there is evidence that the aPTT becomes prolonged by dabigatran, rivaroxaban, apixaban and edoxaban, there are varying results depending on the reagents used and no standard calibration is available. It is, however, a readily available test, and a normal aPTT would suggest that haemostatic function is not impaired.[16]

The prothrombin time and international normalised ratio (INR) are measures of the extrinsic pathway. Warfarin is well known to increase the prothrombin time and its effect can be reliably measured by the INR. Dabigatran has been shown to have a linear relationship with INR; however, it is not possible to estimate the therapeutic

Table 4. *Comparison of NOACs*[3–6]

	Dabigatran etexilate	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Pivotal trials	AF; RELY ($n = 18\,113$) Low-dose dabigatran; high-dose dabigatran; warfarin Low dose – stroke or embolism: 1.53% vs. 1.69% ($P \leq 0.001$ non-inferiority) Major haemorrhage: 2.71% vs. 3.36% ($P = 0.003$) High dose – stroke or embolism: 1.4% vs. 1.6% ($P = 0.41$) Major haemorrhage: 1.11% vs. 1.69% ($P \leq 0.001$ superior) VTE; RE-COVER ($n = 2564$) Dabigatran vs. warfarin VTE or death: 2.7% vs. 2.5% Any bleeding 16.1% vs. 21.9% RE-NOVATE Hip replacement ($n = 3493$) Dabigatran vs. enoxaparin VTE or death 7.7% vs. 8.8% $P \leq 0.0001$ non-inferior Major bleeding 1.4% vs. 0.9% ($P = 0.40$)	AF; ROCKET-AF ($n = 14\,264$) Rivaroxaban vs. warfarin Stroke and systemic embolism 1.7% vs. 2.2% ($P = 0.01$ superior) Bleeding 14.9% vs. 14.5% ($P = 0.44$) DVT; EINSTEIN-DVT ($n = 3449$) DVT: rivaroxaban vs. warfarin Recurrent VTE 2.1% vs. 3.0% ($P \leq 0.001$ non-inferior) Bleeding 8.1% vs. 8.1% $P = 0.77$ PE; EINSTEIN-PE ($n = 4832$) Rivaroxaban vs. warfarin Recurrent VTE 2.1% vs. 1.8% Major bleeding 1.1% vs. 2.2% RECORD1 ($n = 4541$) Rivaroxaban vs. enoxaparin VTE or death 0.8% vs. 3.4% non-inferior Major bleeding 0.3% vs. 0.1%	AF; ARISTOTLE ($n = 18\,201$) Apixaban vs. warfarin Stroke or systemic embolism 1.27% vs. 1.60% ($P < 0.001$ non-inferior) Major bleeding 2.13% vs. 3.09% ($P < 0.001$) VTE; AMPLIFY ($n = 5395$ Apixaban vs. warfarin Recurrent VTE or associated death 2.3% vs. 2.7% ($P < 0.001$ non-inferior) Major bleeding 0.6% vs. 1.8% ($P < 0.001$ superior) ADVANCE-2 ($n = 3057$) Apixaban vs. enoxaparin VTE or death 15% vs. 24% ($P \leq 0.001$) Major bleeding 4% vs. 5% ($P \leq 0.09$)	AF; ENGAGE-AF-TIMI 48 ($n = 21\,105$) Warfarin vs. high dose edoxaban vs. low dose edoxaban Stroke or systemic embolism 1.5% vs. 1.18% vs. 1.61% ($P = 0.001$ non-inferior) Major bleeding 3.43% vs. 2.75% vs. 1.61% VTE; Hokusai-VTE ($n = 8292$) Edoxaban vs. warfarin Recurrent VTE 3.2% vs. 3.5% ($P \leq 0.001$ non-inferior) Major and non-major bleeding 8.5% vs. 10.3% ($P = 0.004$ superior)
Target	Direct thrombin inhibitor including free thrombin, fibrin-bound thrombin and thrombin induced platelet aggregation	Direct factor Xa inhibitor. No effect on thrombin or platelets	Direct factor Xa inhibitor Indirectly inhibits platelet aggregation	Direct factor Xa inhibitor.

Continued on next page

Table 4. *Comparison of NOACs[3–6] (continued)*

	Dabigatran etexilate	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Absorption	Dabigatran etexilate is a pro-drug of dabigatran. Absolute availability is 6.5% following oral administration. Absorption is slower on the first day post operatively (peak at 6 hours post administration)	Availability is 80–100% following oral administration but lowers on fasting conditions.	Absolute bioavailability is 50% for doses up to 10mg.	Absolute bioavailability is approximately 62%.
Distribution	C_{max} is attained within 0.5–2 hours Volume of distribution is 60–70 L	C_{max} is attained within 2–4 hours Volume of distribution is ~50 L	C_{max} attained within 3–4 hours Volume of distribution is ~21 L	C_{max} is attained in 1–2 hours Volume of distribution is ~107 L
Half-life and elimination	Half-life is around 12–14 hours 85% is renally excreted, increasing the half-life in renal impairment. Faecal excretion accounted for 6%	Half-life is approximately 5–13 hours On administration two-thirds undergo metabolic degradation with half then being eliminated renally and half faecally. One-third is renally excreted without metabolism	Half-life is approximately 12 hours Multiple routes of elimination including 25% renal clearance	Half-life is approximately 10–14 hours Over 70% excreted unchanged, with 35% excreted by the kidneys
Protein binding and dialysis	Low protein binding is observed with moderate tissue distribution 50–60% dialysed with 200 mL min^{-1} over 4 hours	Plasma protein binding is approximately 92–95%. with serum albumin being the main binding site. Owing to high protein binding it is not expected to be dialysed.	Plasma protein binding is approximately 87% Owing to high protein binding it is not expected to be dialysed	Plasma protein binding is approximately 55% and is not expected to be dialysed
Dosing	AF: 110–150 mg twice daily VTE: 110–150 mg twice daily Elective orthopaedic surgery: 150–220 mg daily	AF: 20 mg daily VTE: 15 mg twice daily for 21 days then 20 mg daily Elective orthopaedic surgery: 10 mg daily	AF: 5 mg twice daily VTE: 10 mg twice daily for 7 days then 5 mg twice daily Elective orthopaedic surgery: 2.5 mg twice daily	AF: 60 mg once daily VTE: 60 mg once daily
Interactions	Concomitant use of anticoagulants should be avoided. Strong P-glycoprotein (P-gp inhibitors such as ketoconazole, ciclosporin, intraconazole and dronedarone are contraindicated. Mild P-gp inhibitors such as amiodarone, verapamil, quinidine, clarithromycin and tigarelor may increase dabigatran exposure	Concomitant use of anticoagulants should be avoided. CYP3A4 and P-gp inhibitors such as ketoconazole or ritonavir increase concentration of rivaroxaban and inducers cause decreased levels	Concomitant use of anticoagulants should be avoided. CYP3A4 and P-gp inhibitors such as ketoconazole are expected to increase levels and inducers are likely to cause decreased levels.	Concomitant use of anticoagulants should be avoided. P-gp inhibitors such as ciclosporin and ketoconazole are expected in increase levels. Reduced levels with P-gp inducers

Table 5. *Using renal function to time dosing of dabigatran*[4]

Renal function (estimated glomerular filtration rate in mL min^{-1})	Timing of last dabigatran dose before surgery
≥ 50	2 days
30–50	4 days
≤ 30	> 5 days

Table 6. *AAGBI Recommendations related to drugs used to modify coagulation*[15]

Drug	Time to peak effect	Elimination half-life	Acceptable time after drug for block performance	Administration of drug while spinal or epidural catheter in place	Acceptable time after block performance or catheter removal for next drug dose
Warfarin	3–5 days	4–5 days	INR 1.4 or below	Not recommended	After catheter removal
Rivaroxaban prophylaxis (creatinine clearance > 30 mL min^{-1})	3 hours	7–9 hours	18 hours	Not recommended	6 hours
Rivaroxaban treatment (creatinine clearance > 30 mL min^{-1})	3 hours	7–11 hours	48 hours	Not recommended	6 hours
Apixaban prophylaxis	3–4 hours	12 hours	24–48 hours	Not recommended	6 hours
Dabigatran prophylaxis or treatment					
Creatinine clearance > 80 mL min^{-1}	0.5–2 hours	12–17 hours	48 hours	Not recommended	6 hours
Creatinine clearance 50–80 mL min^{-1}	0.5–2 hours	15 hours	72 hours	Not recommended	6 hours
Creatinine clearance 30–50 mL min^{-1}	0.5–2 hours	18 hours	96 hours	Not recommended	6 hours

effect based on the INR and, therefore, the INR is not suitable for monitoring. Rivaroxaban, apixaban and edoxaban also increase the prothrombin time; however, again, this effect is unreliable and varies depending on the reagents used. Similarly to using the aPTT, the prothrombin time can be used as an adjunct before surgery to confirm if haemostatic function is impaired in patients on NOACs.[16]

The thrombin time reflects the activity of thrombin in the plasma. The amount of thrombin present and the concentration of thrombin inhibitors determine the time to clot formation. The thrombin time can be used to detect if there is any dabigatran present. There is a linear relationship between the thrombin time and therapeutic doses of dabigatran. However, at high doses the coagulometers cannot calculate this accurately. The test is therefore not suitable for routine use; however, it can be useful for testing for the presence of dabigatran in an emergency situation. It could be useful to check for a normal thrombin time in patients who are taking dabigatran and need to undergo a high-risk intervention such as epidural cannulation or neurosurgery. Rivaroxaban, apixaban and edoxaban have no effect on the thrombin time.[16]

Novel alternatives

There is slowly emerging evidence in support of the Hemoclot direct thrombin inhibitor assay (Hyphen BioMed, France). The test is based on inhibition of a constant amount of highly purified human alpha-thrombin by adding it to diluted test plasma mixed with normal pooled human plasma. It has shown some accuracy in calculating the quantity of dabigatran present in small study populations. However, over the past 2 years no really convincing evidence for its accuracy has emerged and therefore it is not in widespread use. Cost and availability limit its use in low-income settings.

EMERGENCY REVERSAL MANAGEMENT

Assessing the severity of bleeding is the key to managing bleeding complications. Minor bleeding or moderate bleeding may be managed symptomatically. Major and life-threatening bleeding needs to be managed aggressively and reversal agents, where available, should be considered.

Dabigatran is the only NOAC with a specific reversal agent available at the time of writing. Idarucizumab (Praxbind) is a monoclonal antibody indicated for emergency reversal of dabigatran with the recommended dose being 5 g and reversal effects being evident immediately.[17] Praxbind binds to dabigatran with very high affinity. Binding affinity is approximately 300-fold greater than the binding affinity of dabigatran to thrombin.

The half-life of dabigatran after multiple doses is approximately 14–17 hours and is not dose dependent. This makes dabigatran useful in patients with minor bleeding since withdrawal of the drug may be enough. Since the anticoagulant effect of dabigatran declines in parallel with its plasma concentration, urgent but not emergency surgery may need to be delayed for 12 hours from the last dose of dabigatran.[18] If a specific reversal agent is not available, dialysis may be used for patients on dabigatran. It is expected to remove two thirds of dabigatran within a couple of hours.[19] Rivaroxaban, apixaban and edoxaban are not dialysable because they are highly plasma protein bound.

If no specific reversal agent is available, non-specific haemostatic agents can be used for reversal of excessive bleeding.

- Recombinant factor 7a (NovoSeven) initiates thrombin generation by activating factor 10.
- Four-factor prothrombin complex concentrates (Beriplex, Octaplex) contain large amounts of non-activated vitamin K-dependent factors 2, 7, 9 and 10.
- Three-factor prothrombin complexes (Profilnine SD, Bebulin VH) contain small amounts of non-active factor 7 relating to 2, 9 and 10.
- Activated prothrombin complex concentrate (FEIBA NF) contains activated factor 7 and factors 2, 9 and 10.

Studies of non-specific haemostatic agents have not concluded that one agent or another is better for emergency reversal. No studies have produced results showing complete reversal of anticoagulation using the measurements of aPTT, PT and thrombin time. However, use of non-specific haemostatic agents does reverse parts of the coagulation pathway. Bleeding with rivaroxaban, edoxaban and apixaban is best managed symptomatically with withdrawal of the drug and delaying of the surgery if possible. Most guidelines suggest 48 hours from last dose, which is around four half-lives, for necessary surgery. Alternatively, a regional technique could be considered. For example, a block could be performed 18 hours post prophylactic rivaroxaban dose if the patient has normal renal function.[15]

It should be noted that there are phase II and III trials under way looking at specific NOAC reversal agents. Phase III clinical trials with modified factor Xa (andexanet alfa) are on-going. A molecule with broad activity against various anticoagulants including NOACs (aripazine/ciraparantag) is currently undergoing phase II trials.

REVERSAL OF WARFARIN[20]

Warfarin reversal depends on the presentation of the patient and consideration should be given to the indication for warfarin in the patient. Where possible, procedures should be postponed if the INR is too high rather than routinely reversed.

The reversal agent used for warfarin is a synthetic preparation of phytomenadione (vitamin K_1). The presence of vitamin K is essential for formation of prothrombin, factor 7, factor 9 and factor 10.

- Major bleeding – stop warfarin sodium; give 5 mg phytomenadione (vitamin K_1) by intravenous injection; give four-factor prothrombin complex (factors 2, 7, 9 and 10); if prothrombin complex unavailable, fresh-frozen plasma can be given but is less effective.
- INR > 8.0, minor bleeding – stop warfarin sodium; give 1–3 mg phytomenadione (vitamin K_1) by slow IV injection; repeat dose of phytomenadione if INR still too high after 24 hours; restart warfarin sodium when INR < 5.0.
- INR > 8.0, no bleeding – stop warfarin sodium; give 2.5 mg phytomenadione (vitamin K_1) by mouth using the IV preparation orally; repeat dose of phytomenadione if INR still too high after 24 hours; restart warfarin when INR < 5.0.
- INR 5.0–8.0, minor bleeding – stop warfarin sodium; give 1–3 mg phytomenadione (vitamin K_1) by IV injection; restart warfarin sodium when INR < 5.0.
- INR 5.0–8.0, no bleeding – withhold one or two doses of warfarin sodium and reduce subsequent maintenance dose.
- Unexpected bleeding at therapeutic levels – always investigate possibility of underlying cause, e.g. unsuspected renal or gastrointestinal tract pathology.

CONCLUSION

- In all patients, attention should be paid to the balance between the thrombotic risk posed by stopping a patient's anticoagulation and the risk of bleeding.
- New evidence has shown that patients at low thrombotic risk can safely stop warfarin for a surgical procedure without bridging therapy.
- NOACs can be stopped preoperatively with no bridging because of their predictable and consistent pharmacokinetics. Special consideration should be given to dabigatran, whose excretion can be reduced by poor renal function.
- Thrombin time can be used to detect the presence of dabigatran in an emergency situation.

- Specific emergency reversal of dabigatran is now available and antidotes to other NOACs are expected on the market soon.

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